Remarks

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested.

Initially, applicants would like to thank Examiner MacFarlane for the courtesy extended to the undersigned representative during the telephone interview conducted on July 17, 2009. The substance of the interview is addressed below.

Claims 1-3, 26, 29, and 30 have been amended, and new claims 33 and 34 have been introduced. Claims 1-3, 6, 26, and 29-34 remain pending. No excess claim fees are due with this submission.

Descriptive support for the amendments to the patient, as defined in claims 1 and 26, is provided at page 8, in paragraphs (a) – (d). Treatment for four or more weeks is clearly supported in Examples 1 and 2, where daily administration for four, six, eight, or twelve weeks is described. New claims 33 and 34 are supported by the description of exemplary GHRPs at page 9, and original claim 11. Therefore, no new matter has been introduced by these amendments.

Applicants further submit the meaning of the terms "very high plasma concentration" and "elevated" is definite as used, because persons of skill in the art are fully aware of the meaning of these terms as they apply to cholesterol and/or triglyceride levels and LDL-cholesterol levels, respectively. For example, it is well established that very high plasma concentrations of cholesterol are considered to be greater than 240 mg/dL, very high plasma concentrations of triglycerides are considered to be greater than 400 mg/dL, and elevated LDL-cholesterol is considered to be greater than 160 mg/dL (*see* Jones, "Clinical Diagnosis of Lipid Disorders," *clinical Cornerstone – Hyperlipidemia* 1(1):15-30 (1998) at Table 1, pp. 18 and 23 (copy attached as Exhibit A); Sempos et al., "Prevalence of High Blood Cholesterol Among US Adults," *JAMA* 269(23):3009-3014 (1993) at Tables 1-2 (copy attached as Exhibit B); Ansell et al., "An Evidence-based Assessment of the NCEP Adult Treatment Panel II Guidelines," *JAMA* 282(21):2051-2057 (1999) at Figure (copy attached as Exhibit C)).

The rejection of claims 1-3, 6, 26, and 29-31 under 35 U.S.C. §112 (second paragraph) is overcome by the amendments to claims 1 and 26 to remove the language objected to by the U.S. Patent and Trademark Office ("PTO"). This rejection should therefore be withdrawn.

The rejection of claims 26, 31, and 32 under 35 U.S.C. §112 (first paragraph) for lack of written descriptive support for the genera "CD36 ligand" (as recited in claim 26) and the "Growth Hormone Releasing Peptides (GHRPs) that do not induce secretion of growth hormone" (as recited in claim 31) is respectfully traversed.

As demonstrated by the accompanying Declaration of Sylvie Marleau under 37 C.F.R. § 1.132 ("Marleau Declaration"), the genus of "CD36 ligand that binds to a hexarelin binding site on CD36" and subgenus of "GHRPs that do not induce secretion of growth hormone" were well known in the art prior to August 23, 2002, and their structure/function relationship was known.

The known structure-activity relationship of a number of GHRP analogs is discussed in Deghenghi, "Impervious Peptides as GH Secretagogues," *In Growth Hormone Secretagogues*, Ghigo *et al.* (eds.), pp. 19-14 (1999) ("Deghenghi"). Marleau Declaration, ¶ 6. The GHRPs, as an art-recognized family, include a number of small peptides and peptidomimetic compounds that are derived from the prototypical GHRP-6 peptide. *Id.* One structural feature shared by preferred members of the class of GHRPs is the replacement of D-Trp at position 2 of GHRP-6 with the more stable D-2-methyl Trp derivative (D-Mrp) or beta-naphthylalanine (D-Nal). *Id.* Another structural feature is the prolongation of the chain on the N-terminal side. *Id.* Although not required for activity, many of the GHRPs possess the residues -Phe-Lys or -D-Phe-Lys at the normally C-terminal side, which is amine modified to resist degradation. *Id.*

PCT Publ. No. WO 00/29011 to Mucciolo *et al.* ("Mucciolo") expanded the known structure/function relationship to include other GHRP analogs. Marleau Declaration, ¶ 7. The class of GHRP analogs, as defined in May 2000, was known to include those having the formula:

$$AA^1\text{-}\ AA^2\text{-}\ AA^3\text{-}\ AA^4\text{-Lys-R}$$

where AA^1 is imidazolylacetyl, γ-amino butyryl, isopectinyl, tranexamyl, amino isobutyryl, His-D-Trp, His-D-Mrp, Thr-D-Trp, Thr-D-Mrp, D-Thr-D-Trp, D-Thr-D-Mrp, D-Ala-D-Nal, imidazolylacetyl-D-Trp, imidazolylacetyl-D-Mrp, D-Thr-His-D-Trp, D-Thr-His-D-Mrp, Cys-Tyr-γ-amino butyryl, Ala-His-Trp, Ala-His-D-Mrp, Tyr-Ala-His-D-Trp, Tyr-Ala-His-D-Mrp, D-Ala-D-Trp, or D-Ala-D-Mrp; AA^2 is Ala, D-Nal, D-Lys, D-Mrp, or D-Trp; AA^3 is D-Nal, D-Trp, Mrp, D-Mrp, Phe, or D-Phe; AA^4 is D-Trp, Mrp, D-Mrp, Phe, or D-Phe; and R is Thr-NH_2, D-Thr-NH_2, or -NH_2. *Id.* Mucciolo indicates at page 5, line 31 that compounds containing D-

Mrp are preferred. *Id.* Mucciolo also demonstrates at Figures 1-3 that several of these compounds displace I^{125}-Tyr-Ala-hexarelin. *Id.*

Prior to the priority filing date of the present invention, there was also recognition in the art of a subset of GHRP analogs that lack the ability to induce growth hormone secretion. Marleau Declaration, ¶ 8. These GHRP analogs are identified, for example, in U.S. Patent No. 6,025,471 to Deghenghi ("Deghenghi '471") and Mucciolo. *Id.* One subset of these GHRP analogs that lack the ability to induce growth hormone secretion are characterized by the formula:

A-B-D-Mrp-C-E

where A is H or Tyr; B is a spirolactam, tricyclic or bicyclic structure of the type illustrated at col. 2, lines 7-44 of Deghenghi '471; D-Mrp contains an alkyl group having 1 to 3 carbon atoms, but preferably is methyl; C is Trp-Phe-Lys, D-Trp-Phe-Lys, Mrp-Phe-Lys, D-Mrp-Phe-Lys, Trp-Lys, D-Trp-Lys, Mrp-Lys, D-Mrp-Lys, Ala-Trp-D-Phe-Lys, Ala-Mrp-D-Phe-Lys, Ala-D-Mrp-D-Phe-Lys, D-Lys-Trp-D-Phe-Lys, D-Lys-Mrp-D-Phe-Lys, D-Lys-D-Mrp-D-Phe-Lys, or a tricyclic substituent of the type illustrated at col. 2, lines 53-62 of Deghenghi '471; and E is Lys-NH_2 or -NH_2 (with Lys-NH_2 being preferred when C is the tricyclic structure). Marleau Declaration, ¶ 9. As described at col. 1, lines 35-44 of Deghenghi '471, one common feature is the presence of at least one Lys residue and an Mrp residue. *Id.* That these GHRP analogs lack the ability to induce growth hormone secretion is described in the abstract and at col. 4, line 66 to col. 5, line 2 of Deghenghi '471. *Id.* As described at col. 5, lines 9-11 of Deghenghi '471, the GH-releasing affect of the peptides was assessed according to known procedures. *Id.* The binding abilities of several of these compounds is demonstrated in Deghenghi '471 at Figure 1, showing the results of I^{125}-Tyr-Ala-hexarelin displacement study. *Id.*

Mucciolo also identifies at page 9, lines 1-6, six GHRP analogs that are within the scope of the formula AA^1- AA^2- AA^3- AA^4-Lys-R, but lack the ability to induce growth hormone secretion. Marleau Declaration, ¶ 10. As noted above, procedures were known in the art for discriminating whether a particular GHRP analog induces GH release. *Id.*

Together, Deghenghi, Mucciolo, and Deghenghi '471 identify dozens of preferred GHRP analogs that induce GH secretion and more than a dozen preferred GHRP analogs lack the ability to induce growth hormone secretion. Marleau Declaration, ¶ 11. The structural features of these classes of GHRPs and the correlation between their structure and function were known to persons of skill in the art prior to the priority filing date of the present application. *Id.*

Moreover, the use of GHRPs that lack the ability to induce growth hormone secretion is clearly demonstrated in the application as filed. On page 9 of the application, the peptide EP80317 is identified as one such GHRP, and Examples 1 and 2 demonstrate its efficacy in reducing the lesion area and total plasma cholesterol in patients having multiple risk factors (*apoE* deficient mice fed a high fat, high cholesterol diet) as well as delaying development of fatty streaks induced by poor diet. The difference between the two examples concerns the timing of treatment relative to when the atherogenic diet began. In Example 1, treatment was concurrent, whereas in Example 2 treatment was initiated at various times following initiation of the atherogenic diet (4, 6, or 8 weeks afterward). That the invention can be practiced with other GHRPs that lack the ability to induce growth hormone secretion is supported by the Marleau Declaration, ¶ 13, which indicates that the GHRP EP80318 is able to reduce total aortic lesions, aortic lesion area, and total plasma cholesterol following administration for 6 or 12 weeks to patients having multiple risk factors (*apoE* deficient mice fed an atherogenic diet). For these reasons, the rejection of claims 31 and 32 is improper and should be withdrawn.

As noted in the specification in the paragraph bridging pages 2-3, hexarelin was known to bind to CD36. Claim 26 now recites the use of a "CD36 ligand that binds to a hexarelin binding site on CD36." In addition to the foregoing discussion of GHRPs, which bind to the hexarelin binding site on CD36, another class of agents was also known prior to the priority filing date. These include antibodies that bind to the hexarelin binding site on CD36. One example of such antibodies is the polyconal rabbit anti-rat CD36 (A371) antibody generated in the inventors' laboratory by using the peptide CD36 (164 to 182) coupled to keyhole limpet hemocyanin as immunogen. Marleau Declaration, ¶ 12. The specific anti-CD36 immunoglobulins were purified by affinity on 6% crosslinked agarose coupled to the CD36 (164 to 182) peptide, and the CD36/antibody complex was visualized with a peroxidase-linked goat anti-rabbit antibody and chemiluminescent enhancement.

For these reasons, applicants submit that the knowledge in the art at the time of the invention demonstrates that persons of skill in the art were fully aware of the structure/function relationship among GHRPs generally and with respect to the subset of GHRPs that lack the ability to induce growth hormone secretion. Moreover, because GHRPs were one of several CD36 ligands that bind to the hexarelin binding site on CD36, and persons of skill in the art were aware of other such agents, such as anti-CD36 antibodies, applicants submit that the

specification provides sufficient written descriptive support for the language of claims 26, 31, and 32. Therefore, the rejection should be withdrawn.

The rejection of claims 1-3, 6, 26, and 29-32 under 35 U.S.C. §112 (first paragraph) for lack of enablement is respectfully traversed.

At pages 7-9 of the office action, the PTO asserts that the specification does not enable the treatment of any patient. Applicants have amended claims 1 and 26 to recite that the patient is one who has (i) atherosclerosis, (ii) two or more risk factors selected from the group consisting of obesity, smoking, hypertension, diabetes, mellitus, and family history of premature coronary heart disease, or (iii) a condition selected from the group consisting of very high plasma concentrations of cholesterol and/or triglycerides, hyperlipidemia that is not secondary to underlying disease, and elevated LDL-cholesterol. This is clearly described at page 9 of the application, and supported by the examples, where, as noted above, it is demonstrated using *apoE* deficient mice administered hexarelin or EP80317 that these GHRPs are able to reduce lesion area and total plasma cholesterol, and that EP80317 is able to reduce non-HDL plasma cholesterol.

The patient "in need of such treatment," as recited in claim 32, is an individual that is being treated for atherosclerosis. Thus, this patient population is sufficiently defined and enabled by the specification and the examples.

Contrary to the assertion at pages 9-10 of the office action that hexarelin has no significant effect, hexarelin does indeed have an effect. First, the results of Example 1 demonstrate the ability of hexarelin to prevent development of atherosclerosis and to reduce total plasma cholesterol. Second, the results of Example 2 simply demonstrate the dosage of hexarelin administered for 4 weeks was insufficient in producing a statistically significant reduction in lesion size following atherosclerosis development for 8 weeks prior. A modest decrease was nevertheless measured. The result with EP80317 was also statistically insignificant for the 4 week treatment, but it was significant for the 6 week and 8 week treatments. Unfortunately, 6 and 8 week treatments using hexarelin are not described. Given the results demonstrated with hexarelin and EP80317 in Examples 1 and 2, persons of skill in the art would have expected hexarelin to be effective following longer duration and possibly at higher dosages for the treatment of atherosclerosis.

Thus, the specification does not teach that hexarelin has no significant effect. Rather, it teaches that hexarelin is effective, but less preferred than EP80317.

Finally, given the demonstration that two different GHRPs are effective and the demonstration that a third GHRP is also effective (as described above, and reported in the Marleau Declaration, ¶ 13), one of skill in the art would fully appreciate that the invention can be practiced over the full scope of the invention by intervening at the hexarelin binding site of CD36.

For all these reasons, the rejection of claims 1-3, 6, 26, and 29-32 for lack of enablement should be withdrawn.

The rejection of claims 1 and 6 under 35 U.S.C. § 102(b) as anticipated by Imbimbo et al., "Growth Hormone-releasing Activity of Hexarelin in Humans," *Eur. J. Clin. Pharmacol.* 46:421-425 (1994) ("Imbimbo"), as evidenced by the AHA Heart and Stroke Statistics 2002 Update ("AHA 2002 report"), is respectfully traversed.

Imbimbo reports on the pharmacodynamic, safety, and tolerability results of hexarelin administration to healthy male subjects. Hexarelin was administered in three separate intravenous doses, with a randomly inserted placebo dose; and all injections were separated by "one-week washout periods" (*see* Imbimbo, *study design*). Imbibo does not teach or suggest extending the treatment for four or more weeks, and Imbibo also fails to suggest treating a patient as recited in claim 1. Therefore, the rejection of claims 1 and 6 over Imbibo should be withdrawn.

This submission is accompanied by a request for a one-month extension of time. All fees associated therewith should be charged to deposit account 14-1138. Any overpayment or underpayment should be applied to this same account.

In view of all of the foregoing, it is submitted that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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